Pediatric Focused Safety Review: Intuniv® Extended-Release Tablets (guanfacine hydrochloride ER)

Pediatric Advisory Committee Meeting
September 2013

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Office of New Drugs

Center for Drug Evaluation and Research
Food and Drug Administration

Outline

- Background Information
- Pediatric Studies
- Pediatric Labeling Changes
- Relevant Safety Labeling
- Drug Use Trends
- Previous Safety Reviews
- Adverse Events
- Summary

Background Drug Information
Intuniv® (guanfacine ER)

- **Drug:** Intuniv® (guanfacine hydrochloride)
- **Formulation:** Extended-release tablets, 1, 2, 3 and 4 mg
- **Indication**: Treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients 6 years of age and older, as monotherapy and as adjunctive therapy to stimulant medications
- **Therapeutic Category:** selective central alpha$_{2A}$-adrenergic receptor agonist
- **Sponsor:** Shire Development

Background Drug Information, continued
Intuniv® (guanfacine ER)

- Guanfacine hydrochloride
  - **Immediate** Release (IR): Tenex and generic products
  - **Extended** Release (ER): Intuniv and generic product

Background Drug Information, continued Immediate Release products

- Tenex
  - Original market approval: October 27, 1986
  - Antihypertensive agent, 12 years and older
- Multiple generics

Background Drug Information, continued
Intuniv® (guanfacine ER)

- Original market approval:
  - September 2, 2009, Monotherapy treatment of ADHD (6 years and older)
  - Triggered **prior** PAC safety review, May 2011
- New Indication:
  - February 25, 2011, Adjunctive therapy to stimulant medications (6 years and older)
  - Triggered **this** PAC review

Pediatric Studies
Intuniv® (guanfacine ER)

- 3 placebo-controlled monotherapy clinical studies
  - 2 fixed dose studies in 6-17 year olds
  - 1 flexible dose study in 6-12 year olds
- 1 placebo-controlled adjunctive clinical study in 6-17 year olds

Fixed-Dose Monotherapy Pediatric Studies Intuniv® (guanfacine ER)

- Placebo-controlled, double-blind studies in pediatric patients, 6-17 years of age, with ADHD
  - Study 1 evaluated 2, 3 and 4 mg of Intuniv® daily for 5-weeks (n=345)
  - Study 2 evaluated 1, 2, 3 and 4 mg of Intuniv® daily for 6-weeks (n=324)
- Doses titrated to target fixed dose
- Primary efficacy outcome: change from baseline to endpoint in ADHD-Rating Scale (RS)-IV.

Fixed-Dose Monotherapy Pediatric Studies, continued
Intuniv® (guanfacine ER)

- Results:
  - Statistically significant mean reductions in ADHD-RS-IV total scores at endpoint for Intuniv® compared to placebo.
  - Dose-responsive efficacy was evident.
  - Subgroup analyses:
    - No differential response based on gender
    - Treatment effect observed in ages 6-12 years; limited number (~25%) ages 13-17 years and dosing may have been suboptimal based on exposure

Flexible-Dose Monotherapy Pediatric Study Intuniv® (guanfacine ER)

- Double-blind, randomized, placebo-controlled, dose-optimization study.
- Evaluated 1, 2, 3 and 4 mg of Intuniv® daily for 8-weeks in patients 6-12 years of age (n=340)
- Primary efficacy outcome was change from baseline to endpoint in ADHD-Rating Scale (RS)-IV.
- Results:
  - Mean reductions in ADHD-RS-IV total scores at endpoint were statistically significantly greater for Intuniv® compared to placebo.

Adjunctive Therapy Pediatric Study Intuniv® (guanfacine ER)

- 8-week, double-blind, placebo-controlled, dose optimization study in patients 6-17 years of age with ADHD and a sub-optimal response to stimulants (n=455)
- Evaluated 1, 2, 3 and 4 mg Intuniv® once daily when co-administered with psychostimulants
- Doses titrated over a 5-week dose-optimization period to a maximum of 4mg/day

Adjunctive Therapy Pediatric Study, continued Intuniv® (guanfacine ER)

- Primary efficacy outcome was change from baseline to endpoint in ADHD-RS-IV total scores.
- Results: Mean reductions in ADHD-RS-IV total scores at endpoint were significantly greater for Intuniv® given in combination with a psychostimulant, compared to placebo and a psychostimulant, for both morning and evening Intuniv® dosing.

Outstanding Pediatric Research Equity Act Postmarketing Requirements Intuniv® (guanfacine ER)

- Deferred long-term maintenance efficacy and safety study for the treatment of ADHD in pediatric patients ages 6 to 17.

- Deferred (short-term) efficacy and safety study for the treatment of ADHD in adolescent patients ages 13 to 17.

Preliminary Long-Term Safety Data Intuniv® (guanfacine ER)

As of July 28, 2010:

- 54 pediatric patients had entered an open-label long-term extension study
  - 42 of whom were exposed to Intuniv® for ≥6 months
  - 23 of these patients had completed 2 years
- There were no deaths

Selected Pediatric Labeling Changes Intuniv® (guanfacine ER)

- Initial approval, September 2009 – Monotherapy treatment of ADHD (6 years and older)
- February 2011 - Additional indication of adjunctive therapy to stimulant medications 6 years and older
- February 2013
  - Pediatric flexible-dose study information added
  - Dosage and Administration section changed (once daily, either in the morning or evening, at approximately same time each day)
- August 2013 – Hallucinations added to Post-marketing Experience subsection

Relevant Safety Labeling
Intuniv® (guanfacine ER)

Section 2: Dosage and Administration

- (2.7) Dose Adjustment with Concomitant Use of Strong CYP3A4 Inhibitors or Inducers
  - Labeling provides information for Intuniv® dose adjustments when used concomitantly with strong CYP3A4 inhibitors (e.g., boceprevir, clarithromycin) or inducers (e.g., avasimibe, carbamazepine).

Relevant Safety Labeling, continued Intuniv® (guanfacine ER)

Section 5: Warnings and Precautions

- (5.1) Hypotension, Bradycardia, and Syncope
  - Dose dependent decreases in blood pressure and heart rate. Decrease less pronounced over time of treatment.
  - Orthostatic hypotension and syncope have been reported.
- (5.2) Sedation and Somnolence
  - Somnolence and sedation were commonly reported.

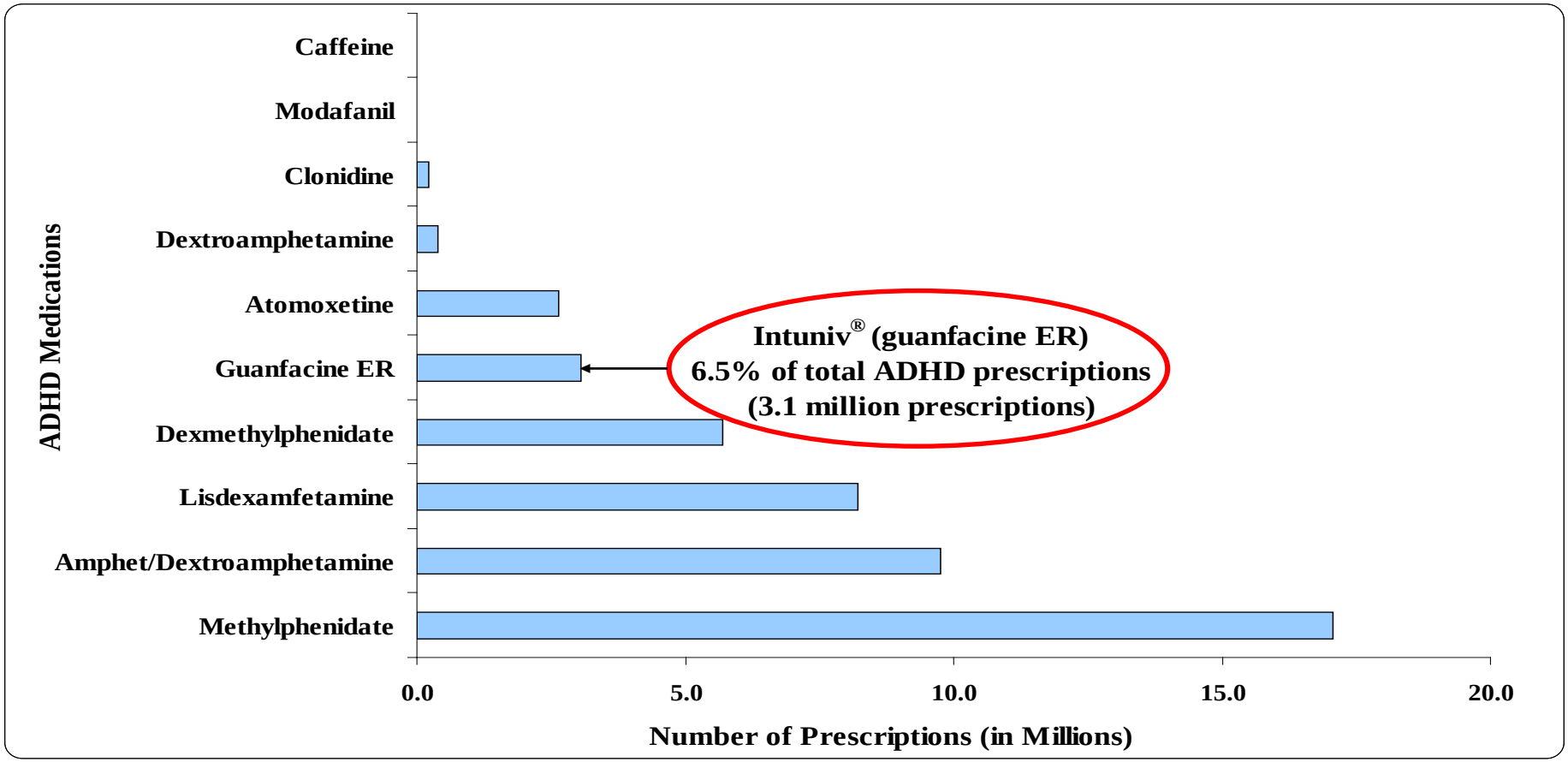
Relevant Safety Labeling, continued
Intuniv® (guanfacine ER)

Section 6: Adverse Reactions

- (6.2) Post-marketing Experience
  - Hallucinations (added August 23, 2013)

ADHD Market: Intuniv® Pediatric Utilization

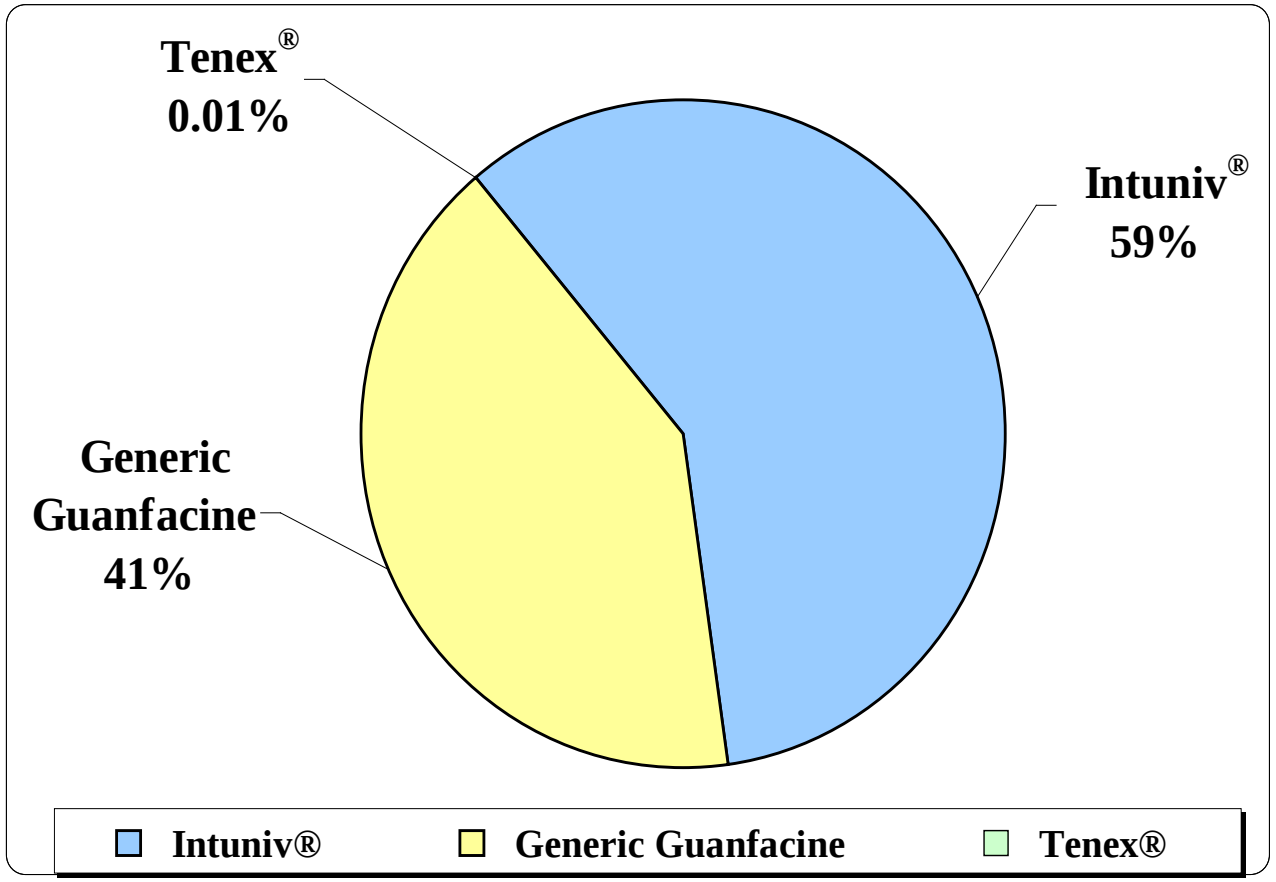
Nationally Estimated Number of Prescriptions for the Top ADHD Molecules (USE Class 64500 and 64700) Dispensed to the Pediatric Population (0-16 years) from U.S. Outpatient Retail Pharmacies, October 2010-June 2012, Cumulative[1]



[1]IMS, Vector One®: National (VONA). October 2010 through June 2012. Data Extracted September 2012.

Proportion of Guanfacine Prescriptions Dispensed to Pediatric Patients (Aged 0-16 years) Stratified by Product, Regardless of Indication

U.S. Outpatient Retail Pharmacy Setting, October 2010 – June 2012, cumulative[1]



[1]IMS, Vector One®: National VONA. October 2010 through June 2012. Data Extracted October 2012.

Intuniv® Drug Utilization, Prescriptions[1] & Patients[2]

U.S. Outpatient Retail Pharmacy Setting, October 2010 – June 2012, cumulative

	Prescriptions N	Prescriptions Share %	Patients N	Patients Share %
INTUNIV® TOTAL	**3,324,118**	***100.0%***	**575,390**	***100.0%***
0-16 years	**3,058,843**	***92.0%***	**519,893**	***90.4%***
0-5 years	123,670	*4.0%*	31,730	*6.1%*
6-11 years	1,934,280	*63.2%*	336,398	*64.7%*
12-16 years	1,000,894	*32.7%*	188,980	*36.3%*
17 years and older	**263,334**	***7.9%***	**63,560**	***11.0%***
Unspecified Age	**1,941**	***0.1%***	**797**	***0.1%***

*** Patient age subtotals** may not sum exactly due to patients aging during the study ("the cohort effect"), and may be counted more than once in the individual age categories. For this reason, summing across time periods or patient age bands is not advisable and will result in overestimates of patient counts.

[1]IMS, Vector One®: National VONA. October 2010 through June 2012. Data Extracted September 2012.
[2]IMS, Total Patient Tracker. October 2010 through June 2012. Data Extracted September 2012.

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Intuniv® Drug Utilization
Prescribing Specialty[1] and Diagnosis[2]
October 2010 – June 2012, cumulative

- Top prescribing specialty for Intuniv® was Psychiatry (44% of prescriptions)
  - **Pediatricians** accounted for 29% of Intuniv® prescriptions
- Top diagnosis code in pediatric patients aged 0-16 years: "Attention Deficit Disorder"

[1]IMS, Vector One®: National (VONA) October 2010 through June 2012. Data Extracted August 2012.
[2]Encuity, Physician Drug and Diagnosis with Pain Panel. October 2010 through June 2012. Data Extracted September 2012.

Concomitant Drug Therapy with Intuniv®

U.S. Office-Based Physician Survey Data[1]

October 2010 – June 2012, cumulative

	Uses N	*Share %*	95% Confidence Interval
TOTAL USES	**1,241,000**	***100.0%***	**1,075,000 - 1,408,000**
0-5 years	**74,000**	***5.9%***	**33,000 - 114,000**
Intuniv	**74,000**	***100.0%***	**33,000 - 114,000**
Used Alone	62,000	*84.6%*	25,000 - 99,000
Vyvanse	5,000	*6.7%*	<500 - 15,000
Focalin XR	4,000	*4.9%*	<500 - 13,000
Fluoxetine	3,000	*3.8%*	<500 - 11,000
6-11 years	**595,000**	***47.9%***	**480,000 - 710,000**
Intuniv	**595,000**	***100.0%***	**480,000 - 710,000**
Used Alone	285,000	*47.9%*	205,000 - 365,000
Vyvanse	102,000	*17.1%*	54,000 - 149,000
Concerta	81,000	*13.7%*	39,000 - 124,000
Adderall XR	31,000	*5.3%*	5,000 - 58,000
Risperdal	30,000	*5.1%*	4,000 - 57,000
All Others	96,000	*16.1%*	49,000 - 142,000
12-16 years	**387,000**	***31.2%***	**294,000 - 480,000**
Intuniv	**387,000**	***100.0%***	**294,000 - 480,000**
Used Alone	172,000	*44.6%*	110,000 - 234,000
Concerta	61,000	*15.7%*	24,000 - 98,000
Vyvanse	60,000	*15.5%*	23,000 - 96,000
Adderall XR	38,000	*9.7%*	9,000 - 66,000
Risperdal	34,000	*8.7%*	6,000 - 61,000
All Others	83,000	*21.4%*	40,000 - 126,000
17 years and older	**145,000**	***11.7%***	**88,000 - 202,000**
Unspecified Age	**40,000**	***3.3%***	**10,000 - 70,000**

[1]Encuity Research, LLC, Treatment Answers™. October 2010 through June 2012. Data Extracted May 2013.

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[1]Encuity Research, LLC, Treatment Answers™. October 2010 through June 2012. Data Extracted May 2013.

Concomitant Drug Therapy with Intuniv® Among Patients Aged 0-5 years old

U.S. Office-Based Physician Survey Data[1]

October 2010 – June 2012, cumulative

	Uses N	*Share %*	95% Confidence Interval
TOTAL USES	**1,241,000**	***100.0%***	**1,075,000 - 1,408,000**
0-5 years	**74,000**	***5.9%***	**33,000 - 114,000**
Intuniv	**74,000**	***100.0%***	**33,000 - 114,000**
Used Alone	62,000	*84.6%*	25,000 - 99,000
Vyvanse	5,000	*6.7%*	<500 - 15,000
Focalin XR	4,000	*4.9%*	<500 - 13,000
Fluoxetine	3,000	*3.8%*	<500 - 11,000

[1]Encuity Research, LLC, Treatment Answers™. October 2010 through June 2012. Data Extracted May 2013.

Concomitant Diagnoses with Intuniv® Among Patients Aged 0-5 years old

U.S. Office-Based Physician Survey Data[1]

October 2010 – June 2012, cumulative

	Uses N	Share %	95% Confidence Interval
TOTAL USES	**1,241,000**	**100.0%**	**1,075,000 - 1,408,000**
0-5 years	**74,000**	**5.9%**	**33,000 - 114,000**
3140 ATTENTION DEFICIT DIS	**45,000**	**61.2%**	**13,000 - 77,000**
Only Diagnosis	25,000	56.4%	2,000 - 49,000
2969 AFFECT PSYCHOSES NEC/NOS	5,000	10.3%	<500 - 15,000
3128 OTHER CONDUCT DISTURB	5,000	10.1%	<500 - 15,000
4900 BRONCHITIS NOS	4,000	9.1%	<500 - 14,000
4739 CHRONIC SINUSITIS NOS	4,000	9.1%	<500 - 14,000
All Others	6,000	14.2%	<500 - 18,000

[1]Encuity Research, LLC, Treatment Answers™. October 2010 through June 2012. Data Extracted May 2013.

Previous Safety Reviews, guanfacine IR

- June 2000: Update of use and safety in pediatric populations with ADHD
  - Most frequent adverse events: central nervous system disorders (convulsions, sedation), psychiatric disorders (mania), cardiac disorders (bradycardia) and injury and poisoning
- August 2000: Update of cases reporting sudden death or serious cardiovascular events with concomitant use of guanfacine and psychostimulant
  - No serious adverse cardiac events or death associated with combination

Previous Safety Reviews, guanfacine IR, continued

- April 2001: Review of mania and aggressive behavior
  - Labeling for guanfacine IR updated (postmarketing adverse events)

- June 2007: Review in response to the pending guanfacine ADHD NDA
  - No new signals for significant adverse events identified
  - Confirmed syncope signal

Previous Safety Reviews, guanfacine ER

- May 2011 – Intuniv® PAC presentation
  - Pediatric adverse event reports: 47 serious cases including 2 fatalities
    - Fatalities (n=2)
      - 9 year-old male with reported cause of death, sudden unexplained death in epilepsy
      - 16 year-old male with reported cause of death, accidental acute “poly-drug toxicity” involving the combined effects of dextromethorphan and morphine
  - No new safety signals were identified
  - PAC asked about concomitant medications and reasons for use/comorbidities

Total Number* of Intuniv® (guanfacine ER) Adverse Event Reports Since Prior OSE Review (October 1, 2010 through June 30, 2012)

	All reports (US)	Serious**(US)	Death (US)
Adults (≥ 17 yrs.)	7 (7)	6 (6)	0 (0)
Pediatrics (0-16 yrs.)	143 (142)	136 (135)	1 (1)
Unknown Age (Null values)	63 (63)	60 (60)	2 (2)***
All Ages	213 (212)	202 (201)	3 (3)

*May include duplicates and have not been assessed for causality

**Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening events, hospitalization (initial or prolonged), disability, congenital anomaly and other serious important medical events.

***One pediatric case identified and determined to be the same 16-year-old male fatal case from the May 2011 Intuniv® PAC Presentation

Selection of Serious Pediatric AERS Cases, Intuniv® (guanfacine ER), Oct. 1, 2010 – June 30, 2012

Total number of serious pediatric reports (n=136)
Pediatric (0-16 years) reports with a serious outcome, including 1 death (n=136)

Duplicate reports (n=8)
-Including 0 deaths

Unduplicated reports (n=128)
-Including 1 death

Excluded Reports (n=5)
-Reported adverse event temporally associated with another drug (n=3)
-Reported an unspecified adverse event or no adverse event reported (n=2)

Pediatric serious cases (n=123, including 1 death)

Characteristics of Serious Pediatric Cases Intuniv® (guanfacine ER) (n=123)

- Gender (n=117)
  - Male (n=77)
  - Female (n=40)
- Age (n=123)
  - 2-5 years (n=9)
  - 6-11 years (n=86)
  - 12-16 years (n=28)

Characteristics of Serious Pediatric Cases Intuniv® (guanfacine ER) (n=123), continued

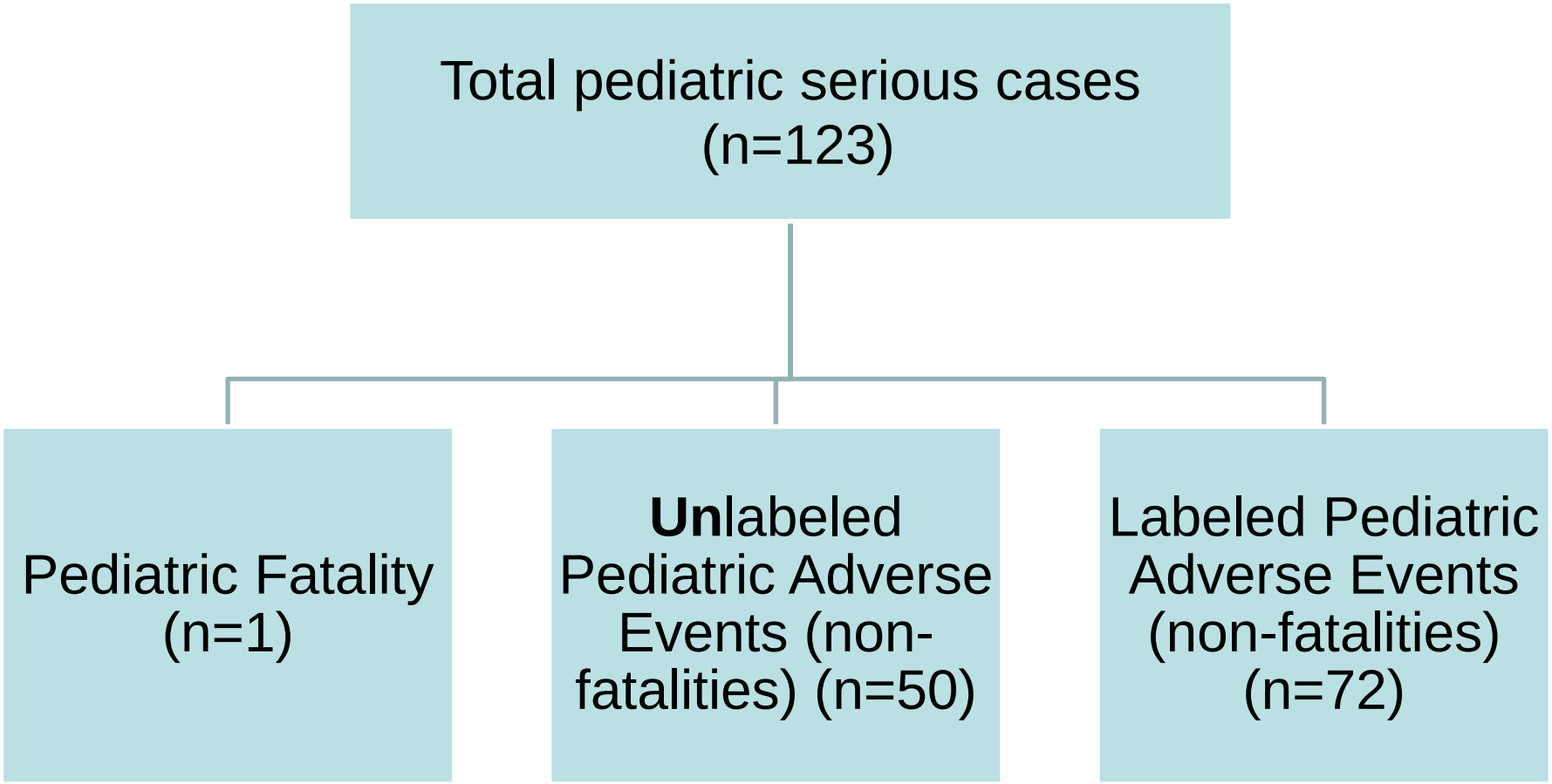
- Primary reasons for use
  - ADHD (n=80)
  - Psychomotor Hyperactivity (n=3)
  - Autism (n=1)
  - Impulsive Behavior (n=1)
  - Unknown (n=38)

Characteristics of Serious Pediatric Cases Intuniv® (guanfacine ER) (n=123), continued

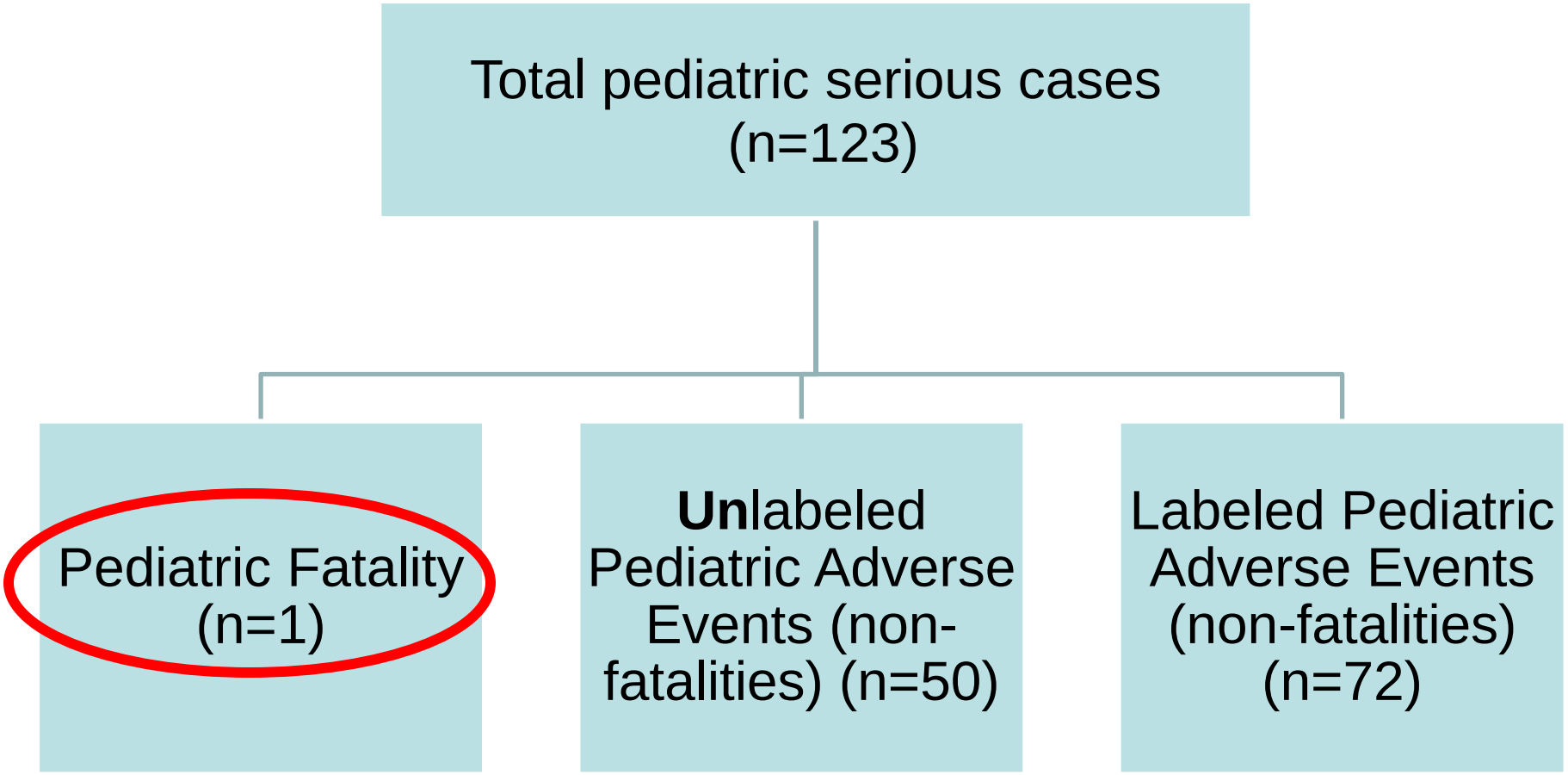
- Primary Serious Outcomes*
  - Death (n=1)
  - Life-threatening (n=7)
  - Hospitalized (n=29)
  - Disability (n=2)
  - Other serious (n=84)

*Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, and other serious important medical events.

Selection of Serious Pediatric AERS Cases Intuniv® (guanfacine ER)



Selection of Serious Pediatric AERS Cases
Intuniv® (guanfacine ER)

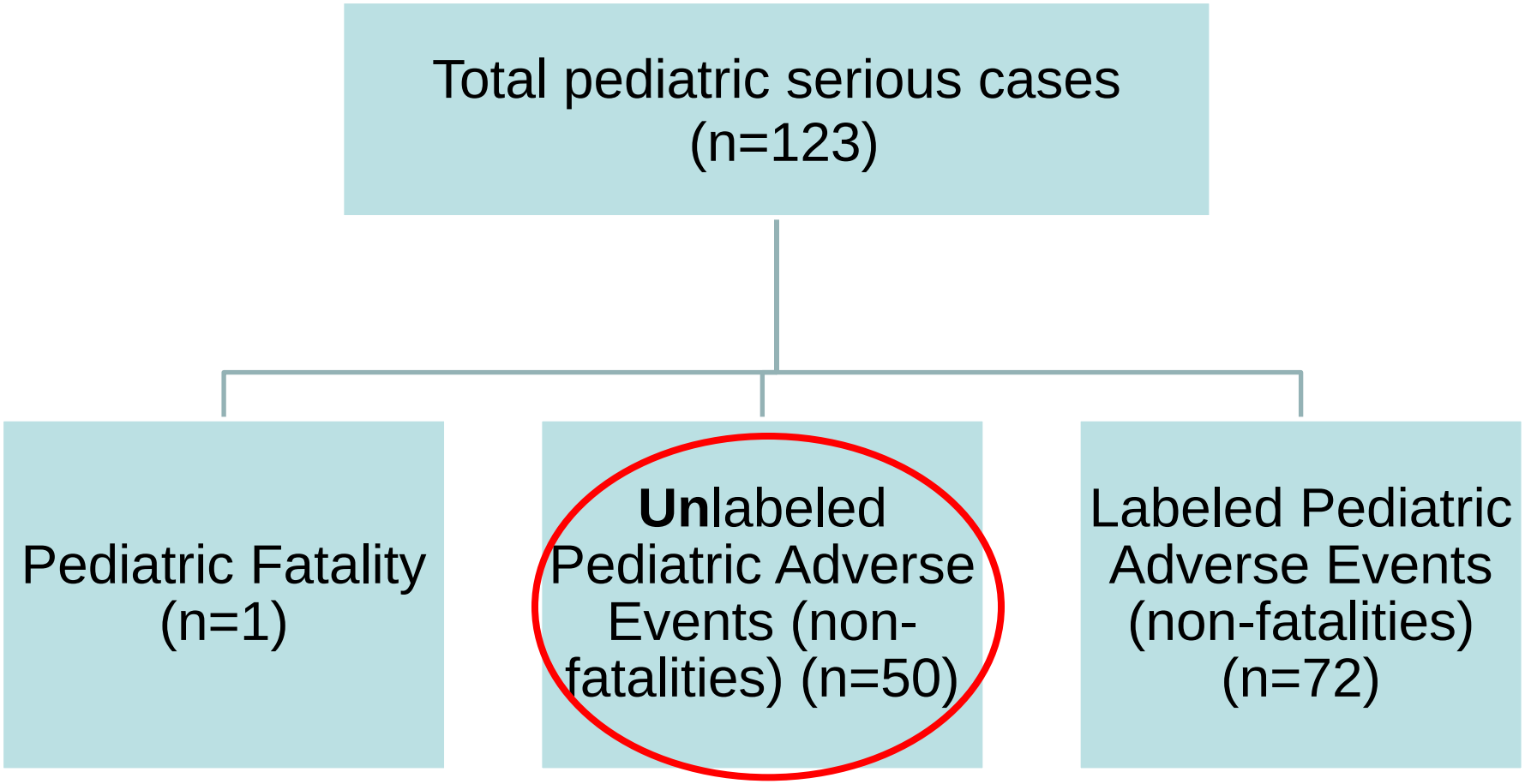


Fatal Adverse Event, 13 year-old male
Oct 1, 2010 – June 30, 2012, Intuniv® (guanfacine ER)

- 13 year-old male with a history of multiple psychiatric disorders including mood disorder.
- For ADHD treatment, received Intuniv® 1mg daily, increased to 4mg daily.
- Patient's mood disorder worsened. He was prescribed fluoxetine, which was discontinued after 1 month for ineffectiveness.
- Patient was then prescribed lamotrigine.
- Intuniv® was decreased to 2mg daily.
- 1 month after that patient committed suicide* (hanging).

**Unlabeled adverse events are underlined on this and subsequent case description slides*

Selection of Serious Pediatric AERS Cases
Intuniv® (guanfacine ER)



Serious Non-Fatal Unlabeled Pediatric Adverse Events Intuniv® (guanfacine ER) (n=50)

- Psychiatric (n=20)
- Nervous system (n=7)
- Gastrointestinal (n=5)
- Cardiac (n=4)
- Other unlabeled (n=14)

Serious Non-Fatal Unlabeled Pediatric Adverse Events Intuniv® (guanfacine ER) (n=50)

- Psychiatric (n=20)
- Nervous system (n=7)
- Gastrointestinal (n=5)
- Cardiac (n=4)
- Other unlabeled (n=14)

Serious Non-Fatal Unlabeled Pediatric Adverse Events, Psychiatric Intuniv® (guanfacine ER)

- Psychiatric (n=20)
  - Self-injurious ideation, suicide attempt, suicidal behavior, or suicidal ideation (n=12)
  - Aggression (n=3)
  - Homicidal ideation/Physical assault (n=3)
  - Other psychiatric adverse events (n=2)
    - Memory loss (n=1)
    - Somnambulism (n=1)

Serious Non-Fatal Unlabeled Adverse Events: Self-Injurious ideation, suicide attempt, suicidal behavior, or suicidal ideation (n=12) Intuniv® (guanfacine ER)

- Gender
  - Males (n=8)
  - Females (n=4)
- Median age: 9 years (Range: 6-16 years)
- Reasons for Intuniv® Use
  - ADHD (n=6)
  - Hyperactivity (n=1)
  - Impulsive behavior (n=1)
  - Not specified (n=4)

Serious Non-Fatal Unlabeled Adverse Events: Self-Injurious ideation, suicide attempt, suicidal behavior, or suicidal ideation (n=12), continued Intuniv® (guanfacine ER)

- Median daily Intuniv® dose: 2 mg (Range: 1mg-26mg)
  - Specified for n=10
- Median time to onset of event following initiating Intuniv®: 8 days (Range: 3 days-10 months)
  - Specified for n=7
- Reported duration of Intuniv® treatment: 3 days, 2 weeks, 1 month
  - Specified for n=3

Serious Non-Fatal Unlabeled Adverse Events: Self-Injurious ideation, suicide attempt, suicidal behavior, or suicidal ideation (n=12), continued Intuniv® (guanfacine ER)

- Reported abatement of events after Intuniv® stopped **(n=1)**
  - 16 year-old male with "ADD" "took a number of pills" and "said he had no reason to live" after 2.5 days of Intuniv® 1 mg daily. No previous incidents of suicide attempt or known suicidal thoughts. Treatment with Intuniv® discontinued after 3 days of use and event resolved. 5 days after event "he is in disbelief and can't resolve why he did this."

Serious Non-Fatal Unlabeled Adverse Events: Self-Injurious ideation, suicide attempt, suicidal behavior, or suicidal ideation (n=12), continued Intuniv® (guanfacine ER)

- Confounded by concomitant medications labeled for suicidal ideation, concurrent aggression, depression or obsessive-compulsive disorder, or a history of suicide attempt **(n=4)**
- Continued Intuniv® treatment **(n=2)**
  - Reduced guanfacine dose from 2mg to 1mg (n=1)
  - Resolution of event without Intuniv® dose change (n=1)
- Insufficient information to assess causality **(n=5)**

Serious Non-Fatal Unlabeled Adverse Events: Aggression (n=3) Intuniv® (guanfacine ER)

- For 2 of the cases, both 6 year-old males:
  - Events abated after Intuniv® discontinued
  - Confounded by concomitant medications labeled for aggression or concurrent autistic spectrum disorder
- 7 year-old male discontinued Intuniv®, outcome not reported

Serious Non-Fatal Unlabeled Adverse Events: Homicidal ideation/Physical assault (n=3) Intuniv® (guanfacine ER)

- 6 year-old male with history of severe aggression received Intuniv® 2mg at bedtime for ADHD, and risperidone 0.5 mg 3 times/day for aggression.
  - Within 1 month of starting Intuniv® he experienced homicidal thoughts. Complete blood count, comprehensive metabolic panel, thryroid stimulation hormone level, and prolactin level were within normal limits.
  - Intuniv® was discontinued and event resolved within the month.

Serious Non-Fatal Unlabeled Adverse Events: Homicidal ideation/Physical assault (n=3), continued Intuniv® (guanfacine ER)

- 8 year-old male received Intuniv® 2 mg 4 times/day for ADHD, and an unspecified stimulant (indication not specified).
  - He experienced homicidal ideation after an unspecified duration of treatment.
  - Within same month of adverse event occurring, Intuniv® was discontinued and event resolved.

Serious Non-Fatal Unlabeled Adverse Events: Homicidal ideation/Physical assault (n=3), continued Intuniv® (guanfacine ER)

- 15 year-old male with underlying “antisocial behavior” and concomitant medications (citalopram, mirtazapine, and risperidone), prescribed Intuniv® 3 mg daily, “tried to murder his family”. Additional clinical information not provided.

Serious Non-Fatal Unlabeled Pediatric Adverse Events Intuniv® (guanfacine ER) (n=50)

- Psychiatric (n=20)
- Nervous system (n=7)
- Gastrointestinal (n=5)
- Cardiac (n=4)
- Other unlabeled (n=14)

Serious Non-Fatal Unlabeled Pediatric Adverse Events, Nervous System Intuniv® (guanfacine ER)

- Nervous System (n=7)
  - Dysarthria, hypoesthesia (n=3)
  - Benign intracranial hypertension (n=1)
  - Dyskinesia (n=1)
  - Parkinsonian rest tremor (n=1)
  - 7th nerve paralysis (n=1)
- Reasons for Intuniv® Use
  - ADHD (n=6)
  - Not specified (n=1)

Serious Non-Fatal Unlabeled Adverse Events: Dysarthria, Hypoesthesia (n=3) Intuniv® (guanfacine ER)

- 6 year-old female "slurred her words" during the 3 weeks she received Intuniv® 3 mg daily for ADHD.
  - An unspecified time after initiating Intuniv® she had a seizure.
  - Intuniv® discontinued and events resolved.
  - Intuniv® is labeled for convulsions.
- 7 year-old male experienced hypoesthesia.
  - Case confounded by concomitant medication labeled for hypoesthesia (montelukast).

Serious Non-Fatal Unlabeled Adverse Events: Dysarthria, Hypoesthesia (n=3), continued Intuniv® (guanfacine ER)

- 7 year-old male with no significant medical history and no concomitant medications received Intuniv® for ADHD.
  - 9 days after starting Intuniv® 1 mg daily, Intuniv® increased to 2 mg and he experienced “lethargy, slurring of words, sleeping on and off, and numb cheeks”.
  - Next day he was diagnosed with strep. throat and started amoxicillin.
  - Day after that he had a seizure and went to ER.
  - Intuniv® stopped after 11 days, and all events except for strep. throat, resolved.
  - Amoxicilin and Intuniv® are labeled for convulsions.

Serious Non-Fatal Unlabeled Pediatric Adverse Events Intuniv® (guanfacine ER) (n=50)

- Psychiatric (n=20)
- Nervous system (n=7)
- Gastrointestinal (n=5)
- Cardiac (n=4)
- Other unlabeled (n=14)

Serious Non-Fatal Unlabeled Pediatric Adverse Events, Gastrointestinal Intuniv® (guanfacine ER)

- Gastrointestinal (n=5)
  - Pancreatitis (n=3)
  - Gastric hemorrhage (n=1)
  - Hepatic enzyme increased (n=1)
- Reasons for Intuniv® Use
  - ADHD (n=2)
  - Unknown (n=3)
- Other gastrointestinal adverse events are in labeling include abdominal pain and vomiting.

Serious Non-Fatal Unlabeled Adverse Events: Pancreatitis (n=3), Intuniv® (guanfacine ER)

- 4 year-old male with “severe” ADHD, initially received treatment with “regular” guanfacine and no concomitant medications.
  - 6 months later, changed to Intuniv® which was titrated from 1 mg to 3 mg over 8 months.
  - 4 months after starting Intuniv® 3 mg, he experienced abdominal pain and vomiting, which prevented him from taking Intuniv®; therefore Intuniv® discontinued without a taper.
  - Experienced respiratory arrest, seizure, and rebound hypertension. Admitted to hospital with pancreatitis.
    - Lipase >10,000, Amylase = 1680 (no units provided)
  - No history of trauma. No cardiac or renal etiology identified.
  - Lipase and amylase normalized several days after hospitalization.

Serious Non-Fatal Unlabeled Adverse Events: Pancreatitis (n=3), continued Intuniv® (guanfacine ER)

- 8 year-old male received Intuniv® for unknown indication.
  - Past and concurrent medical history and concomitant medications not reported.
  - 2 months after starting Intuniv® he was hospitalized and diagnosed with pancreatitis, thrombocytosis ("close to 1 million platelets"), and colonoscopy revealed a "inflamed/infectious" finding.
  - Treatment and outcome not reported.

Serious Non-Fatal Unlabeled Adverse Events: Pancreatitis (n=3), continued Intuniv® (guanfacine ER)

- 13 year-old female, received Intuniv® for unspecified indication.
  - No concomitant medications. Past and concurrent medical histories not reported.
  - Unspecified time later she developed acute pancreatitis and was hospitalized.
  - Intuniv® discontinued and event resolved, timing not specified.

Serious Non-Fatal Unlabeled Pediatric Adverse Events Intuniv® (guanfacine ER) (n=50)

- Psychiatric (n=20)
- Nervous system (n=7)
- Gastrointestinal (n=5)
- Cardiac (n=4)
- Other unlabeled (n=14)

Serious Non-Fatal Unlabeled Pediatric Adverse Events, Cardiac Intuniv® (guanfacine ER)

- Cardiac (n=4)
  - Ventricular extrasystoles (n=2)
  - Ventricular tachycardia (n=1)
  - Electrocardiogram QT prolongation (n=1)
- Reasons for Intuniv® Use
  - ADHD (n=3)
  - Unknown (n=1)
- Other cardiac adverse events are in labeling, include palpitations, tachycardia, atrioventricular block, and sinus arrhythmia.

Serious Non-Fatal Unlabeled Adverse Events: Ventricular Extrasystoles (n=2) Intuniv® (guanfacine ER)

- 8 year-old male taking an unspecified dose of Intuniv® lost consciousness at school. EKG in ambulance in route to ER showed premature ventricular contractions.
  - Intuniv® was discontinued.
  - Physician assessed events as "possibly related to Kawasaki's disorder".

- 9 year-old male experienced premature ventricular contractions while being treated with Intuniv® 2mg, methylphenidate, and methylphenidate extended release. Insufficient clinical information provided to assess causality.

Serious Non-Fatal Unlabeled Pediatric Adverse Events Intuniv® (guanfacine ER) (n=50)

- Psychiatric (n=20)
- Nervous system (n=7)
- Gastrointestinal (n=5)
- Cardiac (n=4)
- Other unlabeled (n=14)

Serious Non-Fatal Unlabeled Pediatric Adverse Events, Other Unlabeled Intuniv® (guanfacine ER)

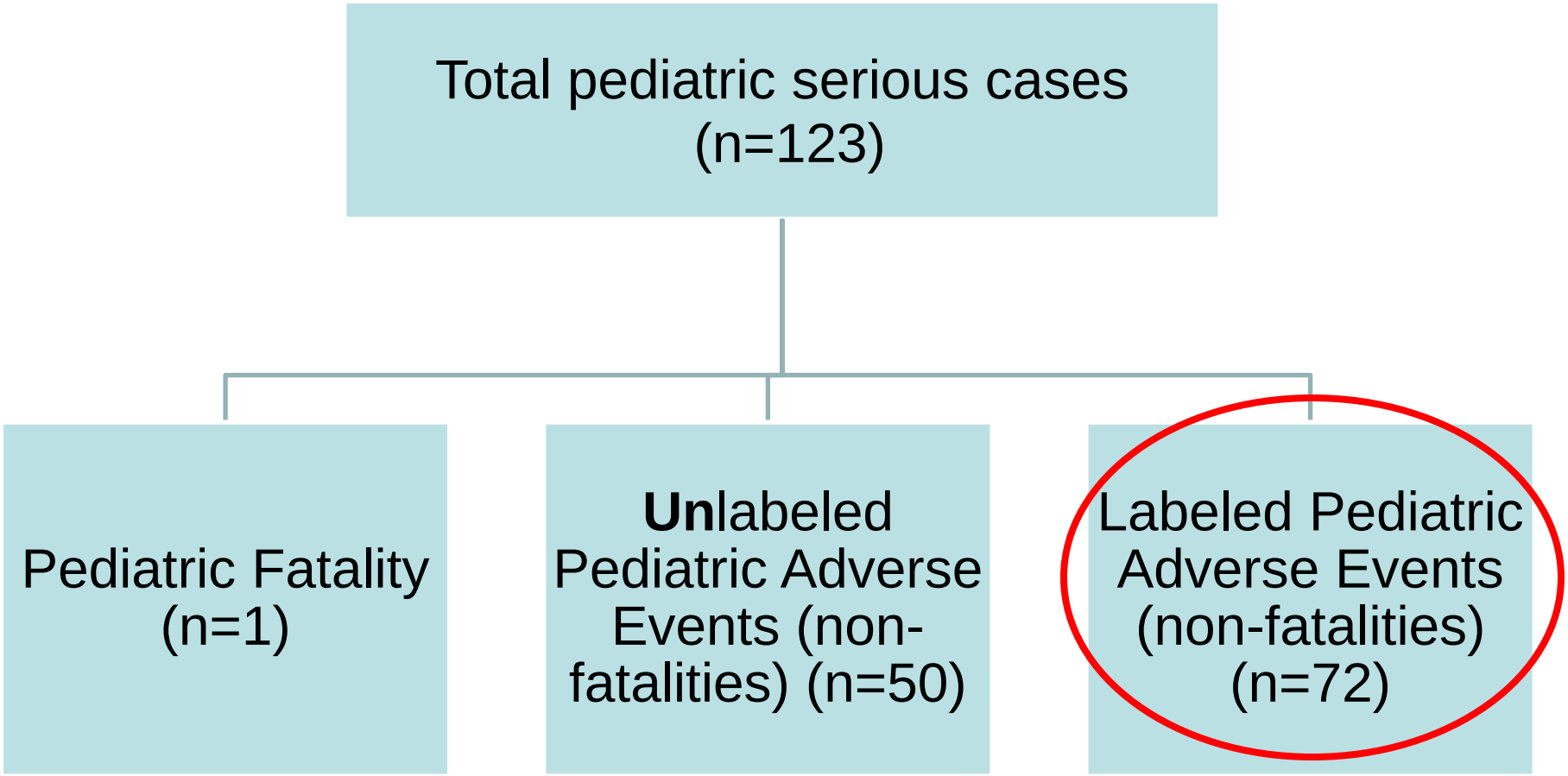
- Other Unlabeled Adverse Events (n=14)
  - Lip swelling (n=2)
  - Eye and face swelling, rash (n=1)
  - Abnormal weight loss (n=1)
  - Transient blindness (n=1)
  - Decreased blood potassium (n=1)
  - Dyspnea, oropharyngeal pain (n=1)
  - Henoch-Schonlein Purpura (n=1)
  - -- Hematoma (n=1)
  - -- Neutropenia (n=1)
  - -- Tinnitus (n=1)
  - -- Strep. Pharyngitis (n=1)
  - -- Epistaxis (n=1)
  - -- Hemorrhagic diasthesis (n=1)

Due to limited number of reports received for each of these events, and limited clinical information in the reports, no conclusions can be made regarding an association between the reported events and Intuniv®.

Serious Non-Fatal Unlabeled Adverse Events: Lip Swelling (n=2), Intuniv® (guanfacine ER)

- 9 year-old female received Intuniv® 2 mg daily, indication not specified. After unspecified duration, she experienced swelling of lips and lips "drooped".
  - Went to ER. Received epinephrine and prednisone. Events resolved. Intuniv® was discontinued.
- 13 year-old female, 2 months after starting doxycycline for acne, received Intuniv® for ADHD; initially 1 mg daily then increased to 3mg daily.
  - 2 months after starting Intuniv® "a small amount of blood was found on the patient's pillow and the patient coughed up a little bit of blood…experienced swelling of her bottom lip."
  - Hemoptysis resolved. Orthodontist saw no evidence of gum or mouth bleeding.
  - Intuniv® and doxycycline continued, and lip swelling persisted.

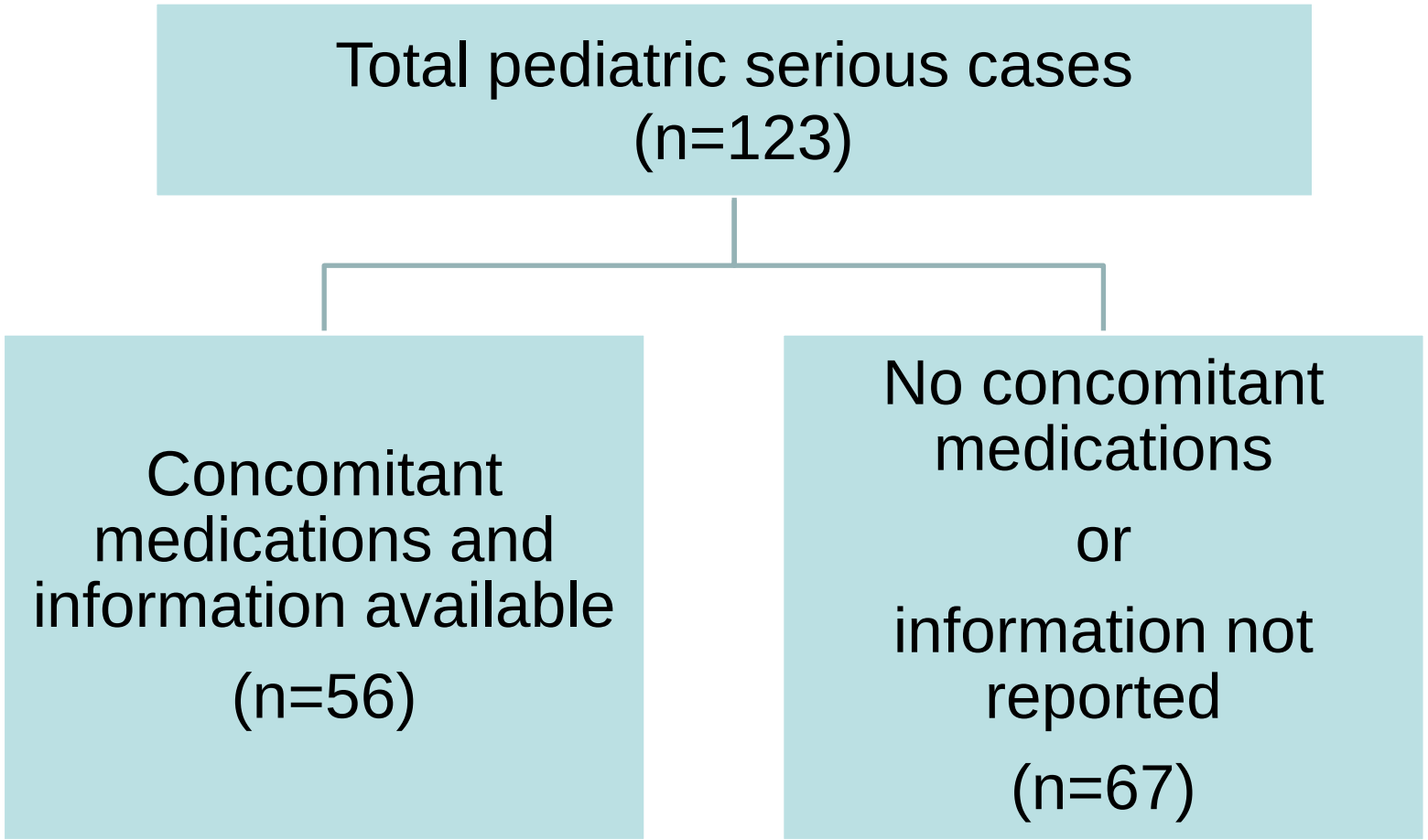
Selection of Serious Pediatric AERS Cases
Intuniv® (guanfacine ER)



Serious Non-Fatal Labeled Adverse Events Intuniv® (guanfacine ER) (n=72)

- Nervous system (n=35)
  - Syncope (n=19), Convulsion (n=11), Somnolence (n=4), Headache (n=1)
- Cardiac (n=19)
  - Bradycardia (n=10), Hypotension (n=4), Atrioventricular block (n=2), Tachycardia (n=2), Chest pain (n=1)
- Psychiatric (n=16)
  - Hallucinations (n=12), Anxiety (n=1), Depression (n=1), Fatigue (n=1), Lethargy (n=1)
- Abdominal pain (n=1)
- Enuresis (n=1)

Serious Pediatric AERS Cases
Intuniv® (guanfacine ER)



Serious Pediatric Cases
Concomitant Medications (n=56)
Intuniv® (guanfacine ER)

- No trend identified between concomitant medications and adverse events reported in the case series.

Serious Pediatric Cases
Concomitant Medications (n=56), continued
Intuniv® (guanfacine ER)

- Example: 4 patients experienced bradycardia

Age (yr)/ Gender	Intuniv indication	CYP450 - 3A4	CYP450 – Other Isoenzymes	Other
6/male	ADHD	Budesonide (major substrate)		Albuterol
11/female	ADHD		Methylphenidate (weak 2D6 inhibitor)	
10/male	ADHD	Divalproex sodium (weak inhibitor)	Divaloproex sodium (substrate and inhibitor of multiple isoenzymes; weak 2A6 inducer)	Levothyroxine
16/male	Not specified	Sertraline (minor substrate; moderate inhibitor)	Sertraline (substrate and inhibitor of multiple isoenzymes)	

Summary Pediatric Focused Safety Review Intuniv® (guanfacine ER)

- This concludes the pediatric focused safety review.
- FDA evaluated hallucination-related adverse events reported with all formulations of guanfacine. Labeling changed (August 2013) to include hallucinations.
- FDA recommends routine monitoring.
- Does the Committee concur?

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Back-Up Slides

Top 5 Diagnoses Associated With the Use of Guanfacine (Excluding Intuniv®)

U.S. Office-Based Physician Survey Data

October 2010 – June 2012[1]

Patients 0-5 years	Patients 6-11 years	Patients 12-16 years
- Attention Deficit Disorder - Other Emotional Child Dis - Early Child Psychosis NOS - Conduct Disturbances NOS - Other Conduct Disturbances	- Attention Deficit Disorder - Other Emotional Child Dis - Early Child Psychosis NEC - Tics - Anxiety States	- Attention Deficit Disorder - Infantile Autism - Early Child Psychosis NES - Bipolar Affective NOS
*NOS: Not Otherwise Classified **NEC: Not Elsewhere Classified		

[1]Encuity Research, LLC., Physician Drug and Diagnosis with Pain Panel. October 2010 through June 2012. Data Extracted October 2012.

Concomitant Diagnoses with Intuniv® Among Patients Aged 0-5 years old

U.S. Office-Based Physician Survey Data[1]

October 2010 – June 2012, cumulative

	Uses N	*Share %*	95% Confidence Interval
TOTAL USES	**1,241,000**	**100.0%**	**1,075,000 - 1,408,000**
0-5 years	**74,000**	**5.9%**	**33,000 - 114,000**
3140 ATTENTION DEFICIT DIS	**45,000**	**61.2%**	**13,000 - 77,000**
Only Diagnosis	25,000	56.4%	2,000 - 49,000
2969 AFFECT PSYCHOSES NEC/NOS	5,000	10.3%	<500 - 15,000
3128 OTHER CONDUCT DISTURB	5,000	10.1%	<500 - 15,000
4900 BRONCHITIS NOS	4,000	9.1%	<500 - 14,000
4739 CHRONIC SINUSITIS NOS	4,000	9.1%	<500 - 14,000
All Others	6,000	14.2%	<500 - 18,000
3138 OTH EMOTIONAL DIS CHILD	**8,000**	**10.5%**	**<500 - 21,000**
2990 INFANTILE AUTISM	5,000	63.7%	<500 - 15,000
3884 OTH ABN AUDITORY PERCEPT	5,000	63.7%	<500 - 15,000
V401 PROB WITH COMMUNICATION	5,000	63.7%	<500 - 15,000
3140 ATTENTION DEFICIT DIS	3,000	36.3%	<500 - 11,000
2998 EARLY CHLD PSYCHOSES NEC	**6,000**	**8.7%**	<500 - 18,000
Only Diagnosis	6,000	100.0%	<500 - 18,000
V401 PROB WITH COMMUNICATION	**5,000**	**6.7%**	<500 - 15,000
3138 OTH EMOTIONAL DIS CHILD	5,000	100.0%	<500 - 15,000
2990 INFANTILE AUTISM	5,000	100.0%	<500 - 15,000
3884 OTH ABN AUDITORY PERCEPT	5,000	100.0%	<500 - 15,000
2990 INFANTILE AUTISM	**5,000**	**6.7%**	<500 - 15,000
3138 OTH EMOTIONAL DIS CHILD	5,000	100.0%	<500 - 15,000
V401 PROB WITH COMMUNICATION	5,000	100.0%	<500 - 15,000
3884 OTH ABN AUDITORY PERCEPT	5,000	100.0%	<500 - 15,000
All Others	**5,000**	**6.2%**	**<500 - 15,000**

[1]Encuity Research, LLC, Treatment Answers™. October 2010 through June 2012. Data Extracted May 2013.

Serious Non-Fatal Unlabeled Adverse Events: Ventricular Tachycardia (n=1) Intuniv® (guanfacine ER)

- 8 year-old male with no significant medical history or concomitant medications received Intuniv® for ADHD.
  - He started Intuniv® at 1 mg daily, and then titrated to 4 mg daily after unspecified duration.
  - While on Intuniv® 4 mg, he experienced “heart skipping beats”, diagnosed as ventricular tachycardia at ER. At ER also experienced bradycardia (heart rate not reported).
  - Diagnosed with AV block of unspecified degree; Holter monitor revealed no abnormalities.
  - Intuniv® decreased to 3 mg daily and all events resolved within the month.
- Tachycardia, bradycardia, and AV heart block are labeled. Ventricular tachycardia specifically is not.

Serious Non-Fatal Adverse Events: Hallucinations (n=12) Intuniv® (guanfacine ER)

- Gender
  - Males (n=8)
  - Females (n=4)
- Median Age: 8 years (Range: 4-10 years)
- Reasons for Intuniv® Use
  - ADHD (n=9)
  - Psychomotor hyperactivity and impulse control disorder (n=1)
  - Not specified (n=2)

Serious Non-Fatal Adverse Events: Hallucinations (n=12), continued Intuniv® (guanfacine ER)

- Median daily Intuniv® dose: 2 mg (Range: 1mg-3mg)
  - Specified for n=10
- Median time to onset of event following initiating Intuniv®: 10 days (Range: 3 days-5 months)
  - Specified for n=7
- Median duration of Intuniv® treatment: 15 days (Range: 3 days-6 months)
  - Specified for n=7

Serious Non-Fatal Adverse Events: Hallucinations (n=12), continued Intuniv® (guanfacine ER)

- Abatement of symptoms with discontinuation of Intuniv® (**n=8**)
  - Confounded by concomitant medications labeled for hallucinations (n=3)
  - Confounded by concurrent bipolar disorder (n=1)
  - Concomitant risperidone use (n=1). Indication for risperidone use in this patient not specified. Risperidone indications include schizophrenia, which may include hallucinations.
  - Incomplete clinical information provided (n=3)

Serious Non-Fatal Adverse Events: Hallucinations (n=12), continued Intuniv® (guanfacine ER)

- Discontinued Intuniv® but did not report outcome (**n=3**)
- Continued Intuniv® and event resolved (**n=1**)
- *FDA conducted a safety review assessing occurrence of hallucination in patients of all ages treated with guanfacine. Labeling changed August 23, 2013.*